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# Thoracic Complications in Patients Undergoing Intraperitoneal Heated Chemotherapy With Mitomycin Following Cytoreductive Surgery

MICHAEL Y.M. CHEN, MD,[1]* CAROLINE CHILES, MD,[1] BRIAN W. LOGGIE, MD,[2]
ROBERT H. CHOPLIN, MD,[1] MARK A. PERINI, BS,[2] AND RONALD A. FLEMING, PharmD[3]

[1]*Department of Radiology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina*
[2]*Department of Surgery, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina*
[3]*Department of Internal Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina*

**Background:** The purpose of this study was to determine the incidence and severity of thoracic reactions in patients undergoing intraperitoneal heated chemotherapy (IPHC).
**Methods:** Forty-two patients who had intraperitoneal disseminated malignancies were treated with cytoreductive surgery (CS) and IPHC. The primary malignancies included carcinoma of the colon (n = 17), stomach (n = 6), appendix (n = 6), pseudomyxoma peritonei (n = 3), mesothelium (n = 2), ovaries (n = 2), jejunum (n = 2), gallbladder (n = 1), urachus (n = 1), and peritoneal carcinomatosis (n = 2). After CS, IPHC with mitomycin (MMC) was administered by perfusion at 40.5°C. After IPHC, multiple radiographs of the chest were reviewed in comparison to the control group.
**Results:** Thoracic complications occurred in 36 patients (86%), including atelectasis in 32 patients (76%), pleural effusions in 27 (64%), pulmonary edema in 10 (24%), pneumonia in 2 (5%), and pneumothorax in 2 (5%). The incidence of thoracic complications in the IPHC group was significantly higher than that of patients in the control group ($P < .05$). Correlations between the prevalence of pleural effusion and the dose of MMC, duration of procedure, and presence of thrombocytopenia were not significant ($P > .05$).
**Conclusions:** Bibasilar atelectasis and pleural effusions are common findings after IPHC with MMC, but most of them do not necessarily warrant intervention. *J. Surg. Oncol. 1997;66:19–23.* 

**KEY WORDS: thorax; chemotherapy, adjuvant; mitomycin C; surgery; peritoneal neoplasms**

## INTRODUCTION

A combination of radical cytoreductive surgery (CS) and intraperitoneal heated chemotherapy (IPHC) with mitomycin (MMC) to treat patients with intraperitoneal disseminated malignancies has been performed in our institution [1–3]. The CS-IPHC combination prolongs

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Correspondence to: Michael Y.M. Chen, M.D., Department of Radiology, Bowman Gray School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157-1088. Telephone: (910) 716-7260 Fax: (910) 716-2029; E-mail: mchen@bgsm.edu

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procedure time and may have a multifactorial effect on thoracic reactions. Although thoracic complications from abdominal surgery and pulmonary reactions from cytotoxicity have been reported, thoracic reactions in patients who undergo heated perfusion with MMC have not been addressed previously. The purpose of this study was to review thoracic reactions in 42 patients who underwent IPHC procedures and to correlate thoracic reactions with the length of procedure, the administered dose of MMC, and the presence of thrombocytopenia. We have previously shown a correlation between thrombocytopenia and serum concentrates of MMC [4]. Patients who had prolonged surgical procedures without heated chemotherapy for abdominal neoplasms during the same time period served as a control group for comparing the thoracic complications in the IPHC group.

## MATERIALS AND METHODS

During a 3-year period, 42 patients (17 women, 25 men) with a mean age of 51 years (range, 18–77 years) who had bulky intraperitoneal disseminated malignancies treated with CS and IPHC were retrospectively and consecutively included in this study. IPHC was repeated in two patients, and only the first IPHC procedure was used in this study. In IPHC procedures, two patients had only a IPHC without CS. The primary locations of cancer included the colon (n = 17), stomach (n = 6), appendix (n = 6), ovaries (n = 2), jejunum (n = 2), urachus (n = 1), gallbladder (n = 1), the peritoneum (pseudomyxoma peritonei in three and mesothelium in two), and peritoneal carcinomatosis of unknown primary (n = 2). Ascites was present in 14 patients, 12 of whom had small amounts of ascites and 2 of whom had large amounts of fluid.

Cytoreductive surgery was performed as judged necessary by the surgeon. All procedures were approved by our Institutional Review Board, and an informed consent was obtained before the start of the procedure. Perfusion cannulae were placed percutaneously in the right and left upper abdomen and return catheters were placed in the pelvis. The skin was closed and the perfusion setup completed. Ringer's lactate solution was used to establish the perfusion circuit (2–3 L) and warmed to an inflow temperature of 40.5°C. Mitomycin 30 mg was added as a bolus dose to the reservoir side (all procedures). After 1 hour, an additional 10 mg of MMC was added to the perfusion (35 procedures). Patient core temperatures were kept below 38°C by passive measures (decreasing room temperature, not warming airway gases, or intravenous fluids). After a perfusion period of 2 hours, the skin was reopened to permit inspection of the abdominal cavity and removal of the cannulae. The abdomen was closed in standard fashion and the patient monitored in the intensive care unit. Average procedure time including CS and IPHC was 515 minutes (range, 285–815 min). Procedure time was <399 minutes in 10 patients, 400–599 minutes in 19 patients, and >600 minutes in 13 patients. Eleven patients had thrombocytopenia after the procedure, and 31 patients had a normal blood count.

A routine preoperative plain film of the chest was obtained as baseline for this study. After IPHC, multiple PA, or AP plain films of the chest, portable or conventional, were obtained for all patients within 3 days postoperatively and thereafter as necessary for some patients. All thoracic complications were tallied by the number of days after procedure and types of complications. All thoracic complications were correlated with the dose administered (30 mg or 40 mg), the length of procedure (<399 min, 400–599 min, or >600 min), and the presence of thrombocytopenia. The radiologic findings were defined. The pleural effusion was categorized into mild, moderate, and severe subgroups depending on the fluid volume in the pleural cavity. Pleural fluid occupying less than one-third of the chest volume is considered a small volume of effusion. Fluid occupying between one-third and two-thirds of the chest volume is categorized as moderate effusion. An amount of fluid equal to more than two-thirds of the chest volume is tallied as severe. Pulmonary atelectasis refers primarily to small focal opacities on the plain chest radiograph. All radiographic findings are recorded from original X-ray reports. When the radiologists interpreted the radiographs, they did not know the details of the procedure and were not aware of this project.

A control group of 14 patients (11 women, 3 men) with a mean age of 49 years (range, 34–63 years) who had prolonged CS procedure times for abdominal malignancies was collected during the same period of time. The control group was chosen to reflect surgery of long duration and known association with substantial morbidity. The average procedure time in the control group was 624 minutes (range, 400–1,030 min). The primary locations of surgically treated cancer in the control group included the rectum (n = 10), vagina (n = 2), cervix (n = 1), and anus (n = 1). The Chi-square test was used to correlate the incidence of thoracic complications in the IPHC group and the control group.

## RESULTS

Thoracic complications occurred in 36 patients (86%) who underwent CS and IPHC, and the lungs were clear after six procedures (14%). Eight patients had one complication, 16 had two complications, and 12 had three complications. Atelectasis (Fig. 1) was present in 32 patients (76%), pleural effusions (Fig. 2) in 27 (64%), pulmonary edema (Fig. 3) in 10 (24%), pneumonia in two (5%), pneumothorax in two (5%), and interstitial infiltrates in three (7%). Pleural effusions were small in 22 patients and moderate in five.

Pleural effusions affected the left side in eight patients

Fig. 1. Day 1 in a patient with malignant peritoneal mesothelioma after intraperitoneal heated chemotherapy (IPHC) chest radiograph shows high density in the right lower lung outlined by an oblique fissure (arrowhead) indicating right-lower-lobe atelectasis.

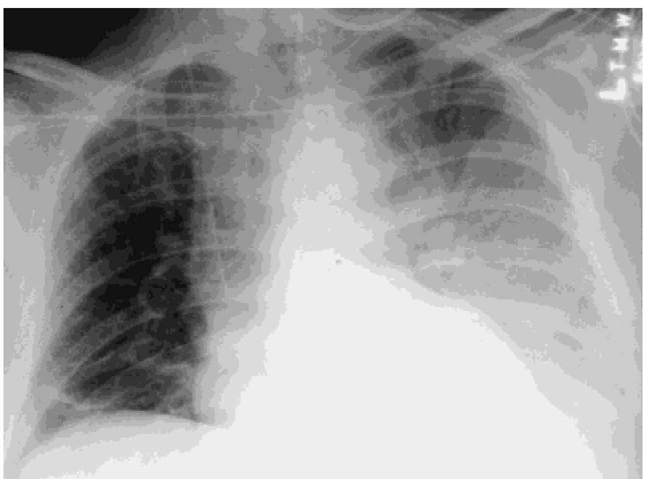

Fig. 2. Day 3 in a patient with colon cancer and peritoneal carcinomatosis after intraperitoneal heated chemotherapy (IPHC); plain chest radiograph shows opacity in the left middle and lower lung, consistent with moderate pleural effusion and possibly associated with atelectasis. Some small densities appear at the left lower lung, indicating atelectasis.

and both sides in 19. Most effusions (20/27, 74%) occurred 1–3 days after IPHC. Pleural effusions lasted <4 days in 17 patients and >5 days in 10 patients.

In the control group (n = 14), radiographic evidence of thoracic reactions was found in eight patients (57%), and the lungs were radiographically clear in six (43%). Atelectasis was present in seven patients (50%), pleural effusions in three (21%), pulmonary edema in four (29%), and pneumonia in three (21%). Two pleural effusions were on the right side, and one was bilateral. One pleural effusion occurred on day 1, one on day 3, and one on day 6. All pleural effusions lasted only 1 day and were small.

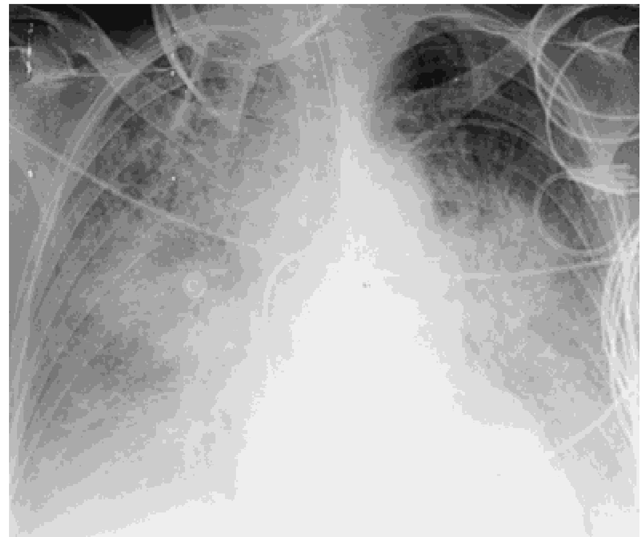

Fig. 3. Day 3 in a patient with colon cancer and peritoneal carcinomatosis; a portable chest radiograph obtained at bedside reveals bilateral diffuse interstitial and air-space opacity with perihilar prominence, indicating pulmonary edema.

The incidence of pleural effusions was significantly higher in the IPHC group than in the control group ($P <$ .01, two-tailed test). Correlations between the prevalence of pleural effusion and the dose (30 mg or 40 mg) of MMC administered ($P >$ .05) were not significant. The prevalence of pleural effusion was correlated to the duration of surgical and perfusion procedure times (<399, 400–599, or >600 min) ($P >$ .05), and presence of thrombocytopenia ($P >$ .05), respectively, and none was statistically significant.

## DISCUSSION

The long-term survival rate for patients with symptomatic peritoneal carcinomatosis is dismal; median survival is <6 months, and the 1-year survival rate is 25%. Abdominopelvic tumor spread is often accompanied by ascites, painful masses, or intestinal obstruction, leading to a miserable quality of life [5]. In vitro study synergistic effect on antitumor cytotoxicity may be created by combining chemotherapy agents such as MMC with hyperthermia [6]. A combination of CS and IPHC has been developed at our institution for patients with peritoneal carcinomas associated with large amounts of ascites. Our preliminary data [1] in 17 patients showed that our median survival rate was 13.4 months, much longer than the rate reported in patients who underwent major surgery for abdominal carcinoma and malignant ascites [5].

Thoracic reactions are commonly seen in patients after major abdominal surgery. A number of postoperative physiological changes, such as diminution of lung volumes, alteration of the normal pattern of ventilation with decreased or absent breaths, decreased clearance of se-

cretions, and impaired mucus transport, may promote the development of pulmonary complications [7]. The pathophysiology of the thoracic reactions in patients undergoing IPHC is uncertain [8]. It may be caused partially by prolonged general abdominal surgery and partially by cytotoxicity during IPHC. Diffuse and focal pulmonary diseases in patients receiving chemotherapy may have many causes, such as infection, the underlying disease, radiation injury, reaction to diagnostic contrast materials, and toxicity from chemotherapeutic drugs. In our study, thoracic reactions were significantly higher in the IPHC group than in the control group, in which the patients had prolonged surgery only. The exact cytotoxic mechanism of these reactions is uncertain.

Basilar atelectasis is the most common finding on the chest film after abdominal surgery, but it is a nonspecific finding. Many predisposing factors, such as previous bronchitis, chronic obstructive lung disease, and prolonged anesthesia time, may affect the incidence of atelectasis. Other factors such as splinting, diminished cough, inappropriate postoperative analgesia, and prolonged patient immobilization in the postoperative period may provide opportunities to develop atelectasis. The prevalence of atelectasis after abdominal surgery is varied. In one review study, if rales alone or radiographic signs alone were used as criteria for the diagnosis of atelectasis, atelectasis was diagnosed in 40–70% of postoperative patients. If clinical symptoms such as rales, fever, sputum production, and radiographic alterations are all required to make the diagnosis, atelectasis occurred in only 20–30% of patients who had upper abdominal surgery, in only 5% of patients who had lower abdominal surgery, and in only 1% of those who had surgery outside the pleural and peritoneal cavity [9]. Potential pathogens may not be confirmed in atelectasis, and the presence of atelectasis does not warrant intervention. In our IPHC group, the incidence of atelectasis (76%) was higher than in the control group (50%), even though the mean procedure time in the IPHC group (515 min) was shorter than in the control group (624 min).

Pleural effusion is the second most common thoracic complication following abdominal surgery. Although pleural effusion may be caused by other factors such as congestive heart failure, pulmonary embolism, pancreatitis, and photodynamic therapy, pleural effusions may be found in as many as 69.5% of patients after upper abdominal surgery and in 34% of patients after lower abdominal surgery [9–11]. Pleural effusions are generally seen on the side of the surgery within 2 weeks after the operation [9]. Postoperative atelectasis may produce pleural effusion by further decreasing the normally negative intrapleural pressure. Peritoneal fluid may enter the pleural cavity through the fenestrations of the diaphragm when diaphragmatic permeability is increased by irritation and when intra-abdominal pressure is increased by ascites or by putting a large volume of fluid into the peritoneal cavity [9].

A potential cause of pleural effusions in our IPHC group is MMC toxicity. The first case of pulmonary toxicity associated with MMC was reported by Orwoll et al. [12]. Since then, MMC has been recognized as a cytotoxic agent that causes pulmonary toxicity [13,14]. Pulmonary toxicities induced by MMC include bilateral interstitial, nodular, or alveolar infiltration, edema, and pleural effusion. Toxic reactions may appear with sudden onset or may present months after therapy [15]. Most thoracic complications occur within 6 months after starting MMC therapy. In one report, 5–12% of patients who received MMC had an interstitial pattern, and pleural effusions occurred 6 months after the therapy [13]. Most symptoms of pulmonary toxicity disappear after MMC is discontinued. Two patients with pulmonary toxicity died when the drug was continued after shortness of breath occurred [13]. There was no correlation between pulmonary toxicity and the age, sex, or underlying disease of the patient [14]. The prevalence of effusion and pulmonary infiltration is not related to the dose of MMC. In one investigation, three patients with normal chest X-ray results received doses of 20–100 mg; however, three other patients who had pulmonary complications had received MMC doses of only 36–40 mg [15].

Interstitial pneumonia appearing as a reticular pattern after MMC administration has been reported by Orwoll et al. [12] in three of 25 patients who had various neoplasms treated with MMC. In Orwoll's group, three patients who received a total dose of 60–156 mg of MMC (20 mg intravenously at 4- or 6-week intervals) had confirmed diffuse alveolar septal edema and mononuclear-cell interstitial infiltrates [12]. Buzdar et al. [15] also reported six patients with pulmonary toxicity after MMC therapy; three of them were normal on chest radiograph and three had bilateral interstitial lung disease. Interstitial lung disease has also been reported in patients 3–15 weeks after receiving chemotherapy with a combination of 5-fluorouracil and MMC [16,17]. The combination of cytotoxic agents may act synergistically to create pulmonary toxicity [16].

The temperature of MMC infusion may affect the efficacy of the treatment, as well as the incidence of thoracic complications. The temperature of MMC infusion to treat peritoneal metastases may or may not be an additional factor in the occurrence of thoracic reactions. Further studies would be necessary to confirm the pulmonary complications in patients with IPHC administered at different temperatures [6].

## CONCLUSION

In our study, bibasilar atelectasis and pleural effusion were significantly higher in patients who underwent CS with IPHC than in the control group. These findings are

possibly related to MMC cytotoxicity, surgical procedure, anesthesia, or increased intraabdominal pressure from ascites or from putting a large volume of fluid into the peritoneal cavity. In the majority of patients, these complications cleared without intervention such as positive-pressure ventilation or thoracentesis.

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